

of the non-elected species, as is the duty according to M.P.E.P. § 803.02 and 35 U.S.C. § 121.

Applicants acknowledge and appreciate that the previous rejection under 35 U.S.C. § 112, first paragraph was withdrawn by the Examiner, and that the Information Disclosure Statement filed December 1, 2004, was considered by the Examiner. See Office Action, pp. 2 and 3.

## II. Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 41, 43, 49-51, and 53-55 under 35 U.S.C. § 35 U.S.C. § 103(a) over U.S. Pat. No. 5,693,791 to Truett ("**Truett I**") in view of U.S. Pat. No. 6,437,119 to Truett ("**Truett II**"), Boeckh et al., *Antibacterial Agents and Chemotherapy*, 1988, 32:1, pp. 92-95 ("**Boeckh**"), Renoud-Grappin et al., *Antiviral Chemistry and Chemotherapy*, 1988, 9, pp. 205-223 ("**Renoud-Grappin**"), and Staroske et al., *Tetrahedron Letters*, 1998, 39, pp. 4917-4920 ("**Staroske**"). Office Action, p. 4.

In the rejection, the Examiner states that **Truett I** teaches the linking of diverse antibiotic moieties via difunctional compounds in order to prepare dimers having the structure A-L-B, where A and B are various antibiotic moieties and L represents a variety of linkers. See Office Action, p. 4. Additionally, the Examiner states that **Truett I** teaches "that the linkage of two antibiotic moieties can create compounds of new activity." *Id.* Furthermore, the Examiner states that **Truett I** "teaches a dimeric compound where one of the antibiotic moieties is ceftazidime, . . . [which is] a beta-lactam antibiotic that reads on the elected species found in claim 53." *Id.* Notably,

however, the Examiner admits that **Truett I** “lacks the teaching of linking vancomycin with ceftazidime. *Id.*

To make up for this deficiency, the Examiner relies upon a combination of four other references: **Truett II**; **Boeckh**; **Renoud-Grappin**; and **Staroske**. According to the Examiner, **Truett II** teaches that “making and using compounds having three antibiotic functionalities linked together, where a quinolone derivative is linked to a beta-lactam, which, in turn, is linked to vancomycin.” *Id.* at p. 5. The Examiner then concludes that **Truett II** “teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound.” *Id.*

The Examiner states that **Boeckh** teaches that it “was well known in the art at the time of filing to use combination therapy with vancomycin and ceftazidime.” *Id.* The Examiner relies upon **Renoud-Grappin** for the suggestion that “one way to achieve effective combination therapy is to covalently link two different drugs,” and that such a combination of drugs could “prevent the emergence of drug-resistant virus strains.” *Id.* Importantly, the Examiner admits that **Renoud-Grappin** deals with compounds that are “anti-virals and not antibiotics.” *Id.* at pp. 5 and 6. Finally, the Examiner relies upon **Staroske** to disclose “dimeric vancomycin compounds [which] exhibit improved antibacterial activity....” *Id.* at p. 6.

Based on the combination of all five of these references, the Examiner contends that :

[I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of [**Truett I**], concerning the linking of diverse antibiotic moieties, and [**Truett II**], where vancomycin and beta-lactam antibiotics are linked as part of a linked, three antibiotic compound, combined with the teaching of

[Boeckh] to perform combination therapy using the drugs, the teaching of [Renoud-Grappin] concerning linking drugs to perform combination therapy and the teaching of [Staroske] concerning vancomycin dimers linked through the amino and carboxy terminus.... One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains.

*Id.* at pp. 6 and 7.

**A. Requirements for Establishing A Prima Facie Case Of Obviousness**

Several basic factual inquiries must be made in order to determine the obviousness or non-obviousness of claims of a patent application under 35 U.S.C.

§ 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), require the Examiner to:

- (1) Determine the scope and content of the prior art;
- (2) Ascertain the differences between the prior art and the claims in issue;
- (3) Resolve the level of ordinary skill in the pertinent art; and
- (4) Evaluate evidence of secondary considerations.

The obviousness or nonobviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18. The M.P.E.P set forth the following tenets of patent law that must be adhered to when making an obviousness rejection:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

M.P.E.P. § 2141 (citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986)).

Thus, in order to carry the initial burden of establishing a *prima facie* case of obviousness that satisfies the *Graham* standard, the Examiner must show (1) that all elements are disclosed by the prior art references, (2) that there exists some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings, and (3) that there is a reasonable expectation of success. See M.P.E.P. § 2143.

**B. No Suggestion or Motivation to Combine and Modify**

With respect to the motivation requirement, the Federal Circuit has held that there must be a clear and particular suggestion in the prior art to combine the teachings of the cited references in the manner proposed by the Examiner. As explained by the Federal Circuit, “[o]ur case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.” *In re Dembiczak* 175 F.3d 994, 999 (Fed. Cir. 1999).

The Examiner can meet the burden of establishing a *prima facie* case of obviousness “only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” *In re Fine*, 837 F.2d 1071, 1072 (Fed. Cir. 1988) (internal citations omitted) (emphasis added). The Federal Circuit

reaffirmed the Examiner's high burden to establish a prima facie case of obviousness in

*In re Sang-Su Lee*, where the Federal Circuit explained that

[t]he need for specificity pervades this authority... the examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.

277 F.3d 1338, 1433 (Fed. Cir. 2002) (internal citations and quotation omitted)

(emphasis added). Moreover, “[t]o establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.” *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) (emphasis added).

For the reasons set forth below, Applicants respectfully submit that the Examiner has failed to meet the burden of establishing a prima facie case of obviousness at least because there exists no suggestion or motivation to combine and modify the five references relied upon in the rejection in the manner proposed by the Examiner. Specifically, further to the tenets of patent law set forth in M.P.E.P. § 2141, after the prior art relied upon by the Examiner “has been considered as a whole,” and “viewed without the benefit of impermissible hindsight vision afforded by the claimed invention,” Applicants respectfully submit that one of ordinary skill in the art would not have been led to combine and modify the prior art as proposed by the Examiner in an attempt to obtain the presently claimed invention.

#### 1. **Truett I**

As set forth above, the Examiner relied on **Truett I** for the general disclosure “that the linkage of two antibiotic moieties can create compounds of new activity.”

Office Action at p. 4. **Truett I** is also relied upon for the proposition that it “teaches a dimeric compound where one of the antibiotic moieties is ceftazidime, . . . [which is] a beta-lactam antibiotic that reads on the elected species found in claim 53.” *Id.*

Applicants respectfully submit that such an interpretation of **Truett I** does not constitute a fair reading of the reference as a whole. As emphasized above, when making an obviousness evaluation, each reference must be considered as a whole. See M.P.E.P. § 2141.

When considering the reference as a whole, one of ordinary skill in the art would appreciate that **Truett I** discloses a large number of antibiotic compounds that may be linked together according to the invention. In fact, **Truett I** discloses nine general classes of antibiotic compounds and 69 specific compounds within those classes that may be linked together. See **Truett I**, col. 1, line 46 through col. 6, lines 27. Faced with the reference’s myriad of choices regarding the selection of the antibiotic compounds, Applicants respectfully submit that the Examiner must provide a basis for the initial selection of a single one of the 69 specific compounds, i.e., ceftazidime, from among all the other antibiotic compounds disclosed in the reference. This the Examiner has not done.

There is simply no discussion in the Examiner’s rejection of how **Truett I** would have led one of ordinary skill in the art to make the specific selection of ceftazidime. Furthermore, after consideration of the teachings of **Truett I** as a whole, Applicants submit that the reference does not contain the specific guidance needed to suggest to one of ordinary skill in the art the selection of ceftazidime over all the other disclosed antibiotics.

Moreover, **Truett I** does not even teach that the general class of glycopeptidic antibiotics, of which vancomycin is a member, can be used according to the disclosed invention. As emphasized above, **Truett I** discloses a laundry list of antibiotics in its specification. This application was filed at a time when vancomycin was well-known in the art, i.e., 1995, yet fails to mention vancomycin or even the general class of antibiotics to which it belongs. Applicants therefore submit that a reading of **Truett I** as a whole would not have motivated one skilled in the art to modify **Truett I** to combine vancomycin with any of the 9 disclosed classes of antibiotics, let alone combine vancomycin with ceftazidime, one of the 69 specifically disclosed compounds, in an attempt to arrive at the presently claimed invention.

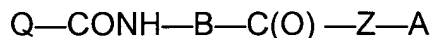
In the face of this limited guidance, and the lack of any disclosure regarding glycopeptidic antibiotics, Applicants respectfully submit that one of ordinary skill in the art reading the general teachings of **Truett I** would have found nothing to motivate or guide them to prepare a compound containing both a beta-lactam and vancomycin moiety as proposed by the Examiner.

## 2. **Truett II**

The Examiner relies upon **Truett II** to assert that the reference “teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound.” Office Action, p. 5. Applicants respectfully submit that this assertion is much too broad when considering the teachings of **Truett II** as a whole.

**Truett II** is directed to the formation of “a single composition from two antibiotics, e.g., from Quinolone antibiotics and Beta-lactam antibiotics, . . . and also with the additional step to add a third antibiotic component [e.g., vancomycin] to the

bi-component composition.” **Truett II**, col. 1, lines 13-20 (emphasis added). Thus, **Truett II**, at best, discloses the linking of a third antibiotic, such as vancomycin, to a bi-component compound that already contains a quinolone moiety linked to a beta-lactam moiety. Such a disclosure can be found, for example, at col. 3, lines 55-65 of **Truett II**, in the description of the synthesis of the general formula



wherein Q is a quinolone, B is a beta-lactam, and A is a third antibiotic, such as vancomycin.

The combination of **Truett I** and **Truett II**, as proposed by the Examiner, fails to take into account the limited teachings of **Truett II**. Specifically, **Truett II** is directed to a bi-component compound already containing two antibiotic moieties to which a third antibiotic moiety is linked. **Truett I** is not concerned with the addition of a third antibiotic moiety to any of the bi-component compounds that may be produced according to the disclosure of **Truett I**. In addition, in the rejection of record, the Examiner has not suggested the addition of such a third moiety to the compounds of **Truett I**.

Rather, the Examiner has suggested the substitution of one of the moieties of **Truett I** with one of the third moieties disclosed in **Truett II**. A reading of these references as a whole would not have led to such a substitution. By removing one of the moieties in **Truett II**, the composition of three antibiotics, which is the focus of the reference, would be destroyed. Accordingly, no motivation would exist for the substitution proposed by the Examiner.



### 3. Reliance Of Kerkhoven Misplaced

Applicants also disagree with the Examiner's reliance on *Kerkhoven* as a means to establishing a prima facie case of obviousness, and submit that *Kerkhoven* has been improperly relied upon, and does not support the Examiner's position.

First, the facts and holding of *Kerkhoven* involved "combin[ing] two compositions each of which is taught by the prior art to be useful for the same purpose." *In re Kerkhoven*, 626 F.2d 846, 848 (C.C.P.A. 1980) (emphasis added). However, in contrast to *Kerkhoven*, the Examiner does not appear to be combining compositions. Rather, in an effort to reproduce Applicant's claimed invention, the Examiner is picking and choosing individual components from isolated disclosures in the cited references. However, "[s]uch piecemeal reconstruction of the prior art patents in light of [Applicant's] disclosure is contrary to the requirements of 35 U.S.C. 103." *In re Wesslan*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

Second, while the individual antibiotic moieties can be found in the prior art, it cannot be true that it would have been obvious to one skilled in the art to combine every antibiotic moiety in every antibiotic composition in every conceivable combination. Such innumerable combinations might be "obvious to try," but "'obvious to try' is not the standard." *Ecolchem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1374, (Fed. Cir. 2000). Nevertheless, it appears to be the Examiner's erroneous belief that any combination of antibiotic moieties in every antibiotic composition is obvious so long as each individual moiety is found that art.

In an attempt to support this position, the Examiner misapplies the holding in *In re Kerkhoven*. In that case, claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dry detergents were held to be prima facie

obvious. However, the instant case is readily distinguishable from *In re Kerkhoven* on its facts. In *In re Kerkhoven*, the two detergent compositions were mixed together in their entirety; here, the Examiner is selecting individual antibiotic moieties from different antibiotic compositions and attempted to combine them. Moreover, it was the “mere mixture” of the two detergent compositions that were at issue in *In re Kerkhoven*; in the present case, the claims involve the linking of different moieties to produce a new compound, and this linking would involve chemical reactions. Notwithstanding these substantial differences, the Examiner incorrectly argues that the holding in *In re Kerkhoven* applies to this case. Applicants disagree, and submit that such an extrapolation of the holding in *In re Kerkhoven* would amount to nothing less than the application of the impermissible “obvious to try” standard as discussed above.

#### 4. **Boeckh, Renoud-Grappin, and Staroske**

In the rejection, the Examiner relies upon these three references to provide additional basis for combining vancomycin with beta-lactam. These three references, however, fail to remedy the deficiencies of **Truett I** and **Truett II**, discussed above. For example, nothing in any of **Boeckh, Renoud-Grappin, and Staroske** would have led one of ordinary skill in the art away from the direct teachings in **Truett II** to employ a three-component antibiotic compound. Accordingly, after consideration of the references in their entirety, one of ordinary skill in the art would not have been led to combine teachings of **Boeckh, Renoud-Grappin, and Staroske** with the teachings of **Truett I** and **Truett II** in the manner suggested by the Examiner.

III. **Conclusion**

Applicants respectfully request reconsideration of the application, and the timely allowance of all pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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